6. (Currently Amended) A chimeric protein heterodimer complex, according to claim ~~2 or~~ 3, wherein the α chain of an integrin is $\alpha 4$ or $\alpha 2$ and the β chain is $\beta 1$.

7. (Currently Amended) A chimeric protein heterodimer complex, according to ~~claim 2 or~~ claim 3, wherein the chimeric protein comprising the $\alpha 4$ of an integrin and the heavy chain of an immunoglobulin comprises the amino acid sequence of SEQ ID NO:1.

8. (Currently Amended) A chimeric protein heterodimer complex, according to ~~claim 2 or~~ claim 3, wherein the chimeric protein comprising the $\alpha 2$ of an integrin and the heavy chain of an immunoglobulin comprises the amino acid sequence of SEQ ID NO:19.

9. (Currently Amended) A chimeric protein heterodimer complex, according to ~~claim 2 or~~ claim 3 wherein the chimeric protein comprising the $\beta 1$ of an integrin and the heavy chain of an immunoglobulin comprises the amino acid sequence of SEQ ID NO:2.

25. (Currently Amended) A drug composition, comprising a chimeric protein heterodimer complex as stated in claim ~~2 or~~ 3.

Please cancel Claim 2 without prejudice and without disclaimer of the subject matter contained therein.

Kindly add the following new Claims 50 and 51:

50. (New) A chimeric protein heterodimer complex, according to claim 3, wherein the α chain of said integrin and the β chain of said integrin are polypeptides derived from an extracellular portion, and wherein the heavy chain of said immunoglobulin is connected to a C terminus of both the α chain and the β chain of said integrin.

51. (New) The chimeric protein heterodimer complex, according to claim 4, wherein the polypeptide derived from an extracellular portion of the α chain of said integrin and the polypeptide derived from an extracellular portion of the β chain of said integrin are linked by a disulfide bond.

Remarks

Applicants note with appreciation the Examiner's entrance of the Request for Continued Examination under 37 C.F.R. 1.114. Claims 2-9, and 25 remain under consideration.

The Applicants have amended Claim 3 to place it in independent form, canceled Claim 2 and added new Claims 50 and 51. Support for new Claim 50 can be found on page 11, lines 19-21 of the Specification where it is stated that "A chemical protein in which the N terminus side of the protein is an integrin molecule and then connected to an immunoglobulin molecule side by side." Further support is found in the phrase:

> "For binding to a DNA coding for the constant region of an immunoglobulin it is desirable to take out a DNA coding for the extracellular portions only of the α chain and the β chain of an integrin. For this purpose, it is preferable to use the PCR method and DNA synthesis. The extracellular portion of either an α chain or β chain refers to the polypeptide sequence on the N terminus side from the portion speculated to be the transmembrane portion. Its partial sequence can also be used as far as the ligand binding capability is retained, but it is preferable to use most of the portion considered to be an extracellular region." (Page 13, line 25 to page 14, line 10 of the Specification).

Support for new Claim 51 can be found on page 22, lines 2-3 of the Applicants' Specification, wherein it is stated that "the heterodimer is linked by the disulfide bond between immunoglobulin heavy chains." Further support is also found in the statement "the obtained integrin-immunoglobulin chimeric protein heterodimer complex is a structurally stabilized complex" (page 23, lines 5-7). Support also resides at page 46, lines 14-16; Example 6, Paragarph 4; Example 7; and page 60, lines 20-22 of the Specification wherein it is articulated that the molecules constituting the heterodimer are linked by a disulfide bond between the IgG heavy chains.

Claim Rejection Under 35 U.S. C. § 103

Claims 2-9, and 25 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Carter et al. (U.S. Patent 5,821,333) in view of Hori et al. (U.S. Patent 5,916,771). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the pending claims, in light of the Specification, show that the Applicants have provided a soluble protein of integrin with its function fully retained. The protein of the Applicants' claims is a heterodimer complex which comprises a chimeric protein comprising a polypeptide selected from an extracellular portion of a α chain of an integrin and a heavy chain of an immunoglobulin (α chain/IgG heavy chain) and a chimeric protein further comprising a polypeptide selected from an extracellular portion of a β chain of an integrin and a heavy chain of immunoglobulin (β chain/IgG heavy chain) wherein these chimeric proteins are linked by a disulfide bond. Applicants respectfully submit that as a result of this structure, the Applicants' protein is a soluble heterodimer complex in which an α chain and a β chain are stably associated even under a solubilizing condition, such as culture solutions or a buffer solution. Despite the presence of a solubilizing condition the heterodimer complex retains function in ligand binding form by linking the polypeptide selected from extracellular portions of the α chain and β chain of the integrin with a disulfide bond. The Examiner's attention is invited to the following passage of the Applicants' Specification which states:

> The supernatant containing α4 • IgG heavey chain-β1 • IgG heavy chain chimeric protein heterodimer complex. (Page 50, line 24 to page 51, line 1). The cultured supernatant of CHO (100 μ1) containing α2 • IgG heavy chain-β1 • IgG heavy chain chimeric protein heterodimer complex (page 61, lines 14-16 (Example 16)).

The aforementioned passages illustrate that the complex is soluble, "so it can be confirmed that the obtained integrin-immunoglobulin chimeric protein heterodimer complex is a structurally stabilized complex." (Page 23, lines 4-7).

The Applicants further invite the Examiner's attention to the following passages of the Applicants' Specification which states:

> The association between both the proteins is stable association through a disulfide bond exisiting in the IgG heavy chains. (Page 48, lines 16-18; page 60, lines 20-22). The binding is $\alpha 4\beta 1$-specific and retains a feature of the binding that it is dependent on cations. (Page 51, lines 8-9; page 62, lines 5-7).

Applicants respectfully submit that the structural stability of an integrin according to the Applicants' claims is a feature which an integrin on a cell membrane was not believed to have.

Furthermore, Applicants submit that the chimeric protein complex of the pending claims has a demonstrated use as a drug, such as a platelet substitute. Applicants respectfully submit that a complete response for medical purposes is obtained only when a soluble integrin, which retains its function, is used. Consequently, the integrin maintains its original function when solubilized to be used for a platelet substitute. In support of the pending claims use as a drug, the Examiner's attention is invited to the Specification on page 23, line 10 to page 33, line 16 and Examples 21 and 22 of the Specification, wherein the medical potential for the claimed protein is evident. Further support demonstrating the use of solubilized integrin as a platelet substitute is shown at Figs. 4 and 5 of Kainoh et al. (copy enclosed), which illustrates the effect of *in vivo* administration of the Applicants' solubilized integrin chimeric protein complex.

Applicants respectfully submit that Carter et al. merely discloses that a heterodimer complex protein is formed by the introduction of a proturberence at the interface of a first polypeptide resulting in a corresponding cavity in the interface of a second polypeptide to form a

hetero-oligomer. Applicants further submit that Hori et al. discloses a heterodimer complex comprising polypeptides linked respectively to an IgG heavy chain and an IgG light chain. Hori et al. merely hints that this particular method may apply to the formation of a heterodimer comprising α and $\beta 1$ integrin and IgG heavy and light chain.

The combination of Carter et al. and Hori et al. only proposes the possibility that a hetero-oligomer may be formed through the binding of a $\beta 1$ integrin polypeptide to an IgG heavy chain and introduction of a cavity and a protruberence therein. Neither Carter et al. nor Hori et al. disclose either: 1) fusing an extracellular portion of an α chain and a extracellular portion of a β chain of an integrin respectively with an IgG heavy, or 2) linking an extracellular portion of an α chain and a extracellular portion of a β chain of a integrin by a disulfide bond to obtain an integrin heterodimer wherein the α chain and the β chain are stably associated to retain function despite the fact that it has been solubilized. In fact, Carter et al. states that "the preferred import residue is not cysteine to prevent possible oxidation or mispairing of disulfide bonds."

Column 9 of Carter et al., states that the "ligand binding domain" is used as a polypeptide which is responsible for binding to a molecule of interest. Consequently, Carter et al. fails to show which partial peptide of an integrin should or could be used. Carter et al. did not clarify which partial structure of an integrin expresses the same function and same ligand binding form as an integrin on a cell membrane.

Column 5 of Hori et al. states that "multimeric protein" is meant to encompass soluble and membrane forms of the receptor. However, at the time the Hori et al. application was filed it was believed that the integrin, which was a membrane binding-type protein, when solubilized resulted in the dissociation of the α chain and a β chains. The resulting dissociation caused loss of function and activity (See Kainoh et al., page 305 right column). The art acknowledges that it

is very difficult to isolate active membrane bound integrins because the α and β chains easily dissociate during the isolation process, resulting in the loss of function. Therefore, it was not known if and how the heterodimer structure, once solubilized, could be retained in order to maintain activity. Therefore, the hypothetical combination of Hori et al. with Carter et al. is inapplicable to the solicited claims. Withdrawal of the rejection is respectfully requested.

In view of the foregoing, Applicants respectfully submit the claims are in condition for allowance which action is respectfully requested.

Respectfully submitted,

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